Differential strain and velocity generation along the right ventricular free wall in pulmonary hypertension

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BACKGROUND: In contrast to the homogeneously distributed deformation properties within the left ventricle, the right ventricular (RV) free wall (RVFW) shows a more inhomogeneous distribution. It has been demonstrated that pulmonary hypertension (PH) results in significant RVFW mechanical delay.

OBJECTIVE: To assess the effect of the degree of pulmonary arterial systolic pressure on the RVFW strain gradient and on myocardial velocity generation.

METHODS: Peak longitudinal strain and velocity data were collected from three different segments (basal, mid- and apical) of the RVFW in 17 normal individuals and 31 PH patients.

RESULTS: A total of 144 RV wall segments were analyzed. RVFW strain values in individuals without PH were higher in the mid and apical segments than in the basal segment. In contrast, RVFW strain in PH patients was higher in basal segments and diminished toward the apex. In terms of RVFW velocities, both groups showed decremental values from basal to apical segments. Basal and mid-RVFW velocities were significantly lower in PH patients than in individuals without PH.

CONCLUSIONS: PH results in significant alterations of strain and velocity generation that occurs along the RVFW. Of these abnormalities, the reduction in strain from the mid and apical RVFW segments was most predictive of PH. It is important to be aware of these differences in strain generation when studying the effect of PH on the right ventricle. Additional studies are required to determine whether these differences are due to RV remodelling.

Key Words: Echocardiography; Pulmonary hypertension; Right ventricular function; Right ventricular strain; Tissue Doppler imaging

Tissue Doppler imaging (TDI) has allowed for better quantification of myocardial function by demonstrating specific regional changes in strain generation and in the development of myocardial velocities (1-4). Significant differences in these two TDI indexes (ie, strain and velocity) have been reported for both the right and left ventricles. These differences are likely explained, in part, by the different loading conditions and compliance properties of these two chambers (5,6). However, equally important are the differences noted in myocardial fibre arrangement between the right and left ventricles (7-9). Regardless of the mechanism(s), it has been described that, in contrast to the homogeneously distributed deformation properties within the left ventricle, strain values are inhomogeneously distributed in the right ventricle and show a reverse baso-apical gradient, reaching their highest values toward apical segments and the outflow tract (7,10).

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Déformation et vitesse différentielles générées au niveau de la paroi libre du ventricule droit dans l'hypertension pulmonaire

HISTORIQUE : Contrairement aux propriétés de déformation distribuées de façon homogène dans le ventricule gauche, la paroi libre du ventricule droit (PLVD) montre une distribution inhomogène. Il a été démontré que l'hypertension pulmonaire (HTP) entraîne un retard mécanique dans la PLVD.

OBJECTIF : Évaluer l'effet du degré de pression artérielle pulmonaire systolique sur le gradient de déformation de la PLVD et sur la vitesse myocardique.

MÉTHODES : Les données de déformation et de vitesse longitudinales de pointe ont été recueillies à partir de trois segments différents de la PLVD (basal, médian et apical) chez 17 sujets sains et 31 patients atteints d'HTP.

RÉSULTATS : En tout, 144 segments de paroi VD ont été analysés. Chez les sujets indemnes d'HTP, les valeurs de déformation de la PLVD étaient plus élevées au niveau des segments médians et apicaux qu'au niveau des segments basaux. En revanche, les valeurs de déformation de la PLVD chez les patients atteints d'HTP étaient plus élevées au niveau des segments basaux et moindres vers l'apex. En termes de vitesse de la PLVD, les deux groupes ont affiché des valeurs décroissantes entre les segments basaux et apicaux. Les vitesses des segments basaux et médians étaient significativement moindres chez les patients atteints d'HTP que chez les sujets indemnes.

CONCLUSION : L'HTP entraîne des altérations significatives de la déformation et de la vitesse observées au niveau de la PLVD. Parmi ces anomalies, la réduction de la déformation des segments médians et apicaux a été la plus prédictive de l'HTP. Il est important de connaître ces différences sur le plan de la déformation générée lorsqu'on veut analyser l'effet de l'HTP sur le ventricule droit. D'autres études devront être réalisées pour déterminer si ces différences sont attribuables au remodelage VD.

Because the Cardiovascular Institute at the University of Pittsburgh (Pittsburgh, Pennsylvania) previously demonstrated that pulmonary hypertension (PH) results in a significant right ventricular (RV) free wall (RVFW) mechanical delay (11), we assessed the effect of the degree of pulmonary arterial systolic pressure (PASP) on the RVFW strain gradient and on myocardial velocity generation to obtain a better understanding of RV failure in PH.

METHODS

Study population

In addition to TDI information, complete echocardiographic data, including an acceptable tricuspid regurgitation signal to estimate RV systolic pressure, were recorded in 31 consecutive patients with a history of PH who were referred for an echocardiographic examination.

Figure 1) Grey-scale four-chamber apical view with the typical orientation of the regions of interest for longitudinal strain measurement. The first sample volume was placed at the right ventricle (RV) base, the second sample volume at the RV mid-wall, and the third sample volume in the apical portion of the RV free wall distal to the insertion of the moderator band. Careful positioning of the region of interest was accomplished by tracking its location in both systole and diastole. LA Left atrium; LV Left ventricle; RA Right atrium

Similar data were also obtained from a group of 17 individuals without a history of heart disease who required an echocardiographic examination; these patients served as controls. Patients were excluded if they had an irregular heart rhythm such as atrial fibrillation, resting wall motion abnormalities, cardiomyopathy, moderate-to-severe valvular heart disease and the presence of a pacer or defibrillator wire in the right ventricle. The institutional review board at the University of Pittsburgh Medical Center approved the study.

Standard echocardiography

All patients underwent a complete transthoracic echocardiographic study including two-dimensional, colour-flow and spectral Doppler imaging as well as tissue strain imaging using a GE Vingmed Vivid 7 system (GE Vingmed Ultrasound, Norway). Standard two-dimensional echocardiographic evaluation of RV size and function was performed (12). In addition, RV end-diastolic and end-systolic areas were measured from the apical four-chamber view to calculate right ventricular fractional area change (RVFAC) (12-14).

To determine the motion and excursion of the annulus, the M-mode cursor was oriented to the junction of the tricuspid valve plane with the RVFW using images in the apical four-chamber view. Maximal tricuspid annular plane systolic excursion (TAPSE) was determined by measurement of the tricuspid annulus from its highest position after atrial ascent to its lowest position during ventricular systole (13).

PASP was estimated by calculating the systolic pressure gradient between the right ventricle and atrium (from the maximum velocity of the tricuspid regurgitant jet using the modified Bernoulli equation) and then adding to this value the estimated right atrial pressure (based on both the size of the inferior vena cava and its change in calibre during respiration) (15,16).

Tissue Doppler imaging

Colour-coded tissue Doppler cine loops were obtained (as routinely performed at the Cardiovascular Institute) from three beats seen in apical

four-chamber views at mean ($\pm$ SD) depths of 14 ± 2 cm with pulse repetition frequency set at 1 kHz, a Nyquist velocity range of plus or minus 16 cm/s and frame rates of 99 ± 9 Hz (17-21). The initial length for longitudinal strain measurement was set at 12 mm and the regions of interest with a length of 20 mm to 24 mm and a width of 6 mm to 8 mm were placed in three different segments of the RVFW (base, mid-wall and apical near the insertion of the moderator band), to measure the peak longitudinal systolic velocities as well as strain (Figure 1). Careful positioning of the region of interest was accomplished by tracking its location in both systole and diastole. This allowed not only adequate alignment with the ventricular wall but also avoided the tricuspid annulus. To standardize measurements, all time intervals were corrected for heart rate (17,18,21,22):

$$\text{Corrected interval} = \frac{\text{Measured interval}}{\sqrt{\text{RR interval}}}$$

Statistical analysis

All echocardiographic parameters were calculated using the commercially available software EchoPAC PC version 6.00 (GE Vingmed Ultrasound) and determined by a single observer. Three measurements were collected from each variable, and the mean and SD of each variable was used for comparison analysis using the two-tailed Student's *t* test for paired and unpaired data, respectively. Linear regression analysis was used to examine relationships between several dependent variables. Univariate analysis between PASP and other echocardiographic variables was also performed. The usefulness of the myocardial strain and velocity to detect PH was assessed using receiver operating characteristic (ROC) curves to provide optimal values for each variable and areas under the ROC curves, which were compared by the method of Hanley and McNeil (23). Finally, a stepwise, multiple linear regression analysis between strain and velocity was performed to determine the independent predictive value of the echocardiographic variables with respect to PH. $P < 0.05$ was considered to be statistically significant.

RESULTS

Basic echocardiographic data

The analysis of both groups of patients revealed that there was no statistically significant difference in terms of age between individuals with normal PASP (age 54 ± 21 years; $\text{PASP} = 31 \pm 7$ mmHg) and patients with PH (age 58 ± 14 years; $\text{PASP} = 81 \pm 20$ mmHg). Patients with PH had a wider QRS interval than control individuals (0.95 ± 0.16 ms versus 0.71 ± 0.9 ms; $P < 0.0001$). No difference in terms of heart rate was noted between the two groups. PH patients also had statistically lower RVFAC ($31 \pm 14\%$ versus $60 \pm 9\%$; $P < 0.0001$) and TAPSE (1.55 ± 0.47 cm versus 2.67 ± 0.46 cm; $P < 0.0001$) than normal controls. Finally, there was no difference in left ventricular systolic function between PH patients and controls (ejection fraction of $61 \pm 5\%$ versus $65 \pm 6\%$; P not significant).

Tissue Doppler imaging data analysis

Peak longitudinal strain and velocity data were collected from three different segments of the RVFW in 17 individuals without PH and in 31 patients with PH. A total of 144 RV segments were analyzed.

TDI results of RV strain and velocities are shown in Table 1. Differences between normal and PH patients with respect to strain along the RVFW are seen in Figure 2A. Two important points can be ascertained from this figure. First, strain values are statistically lower in PH patients than in normal patients. Second, RVFW strain in PH patients was higher in basal segments and diminished toward the apex, contrary to what is seen in normal subjects who show higher strain in the mid and apical RVFW segments than at the base.

In contrast, Figure 2B shows that, for both normal subjects and PH patients, a decremental generation in myocardial velocities can be seen from basal to apical segments. More importantly, this longitudinal reduction in myocardial velocities is more significantly noted in PH patients.

TABLE 1
Tissue Doppler imaging variables

Variable	Controls	Pulmonary hypertension patients	P
Basal RVFW strain, %	-26.1±6.6	-17.4±5.3	0.0001
Mid RVFW strain, %	-32.8±7.09	-17.4±9.4	0.00001
Apical RVFW strain, %	-27.4±6.6	-13.0±7.5	0.00001
Corrected time-to-peak, basal RVFW strain, s	0.41±0.05	0.45±0.11	NS
Corrected time-to-peak, mid-RVFW strain, s	0.38±0.05	0.45±0.12	NS
Corrected time-to-peak, apical RVFW strain, s	0.37±0.03	0.41±0.11	NS
Basal RVFW velocity, cm/s	9.1±1.6	5.7±2.9	0.0001
Mid RVFW velocity, cm/s	6.1±1.3	4.3±2.6	0.02
Apical RVFW velocity, cm/s	3.7±1.4	2.6±1.6	0.02
Corrected time-to-peak, basal RVFW velocity, cm/s	0.18±0.04	0.20±0.07	NS
Corrected time-to-peak, mid RVFW velocity, cm/s	0.18±0.04	0.20±0.07	NS
Corrected time-to-peak, apical RVFW velocity, cm/s	0.18±0.05	0.20±0.08	NS

Data presented as mean ± SD. The negative strain values during ventricular systole represent a reduction in shortening as fibres contract longitudinally. NS Nonsignificant; RVFW Right ventricular free wall

Figure 2) A Box plot graph showing the mean and SD strain along the right ventricular free wall (RVFW) of pulmonary hypertension (PH) and normal (No PH) patients. Strain values are statistically lower in PH patients than in normal patients, and RVFW strain in PH patients is higher in basal segments and then diminishes toward the apex, contrary to what is seen in normal patients who show higher strain in the mid and apical RVFW segments than at the base. The negative strain values represent a reduction in shortening as fibres contract longitudinally. **B** Box plot graph showing the mean and SD myocardial velocities along the RVFW of normal and pulmonary hypertension (PH) patients. A longitudinal reduction in myocardial velocities can be seen from basal to apical segments in both normal and PH patients but it is of greater statistical significance in PH patients

RVFW strain and velocity TDI measurements were then compared with standard echocardiographic values of RV size and systolic function.

TABLE 2
Receiver operating characteristic analysis for basal, mid and apical right ventricular free wall (RVFW) strain generation and myocardial velocity

Variable	Cut-off	AUROC (95% CI)	P
Basal RVFW peak velocity, cm/s	≤7.3	0.833 (0.697–0.925)	0.0001
Mid RVFW peak velocity, cm/s	≤4.6	0.677 (0.527–0.805)	0.0347
Apical RVFW peak velocity, cm/s	≤2.3	0.678 (0.528–0.806)	0.0336
Basal RVFW peak strain, %	≥19.0	0.873 (0.745–0.951)	0.0001
Mid RVFW peak strain, %	≥24.2	0.898 (0.775–0.966)	0.0001
Apical RVFW peak strain, %	≥22.8	0.911 (0.792–0.973)	0.0001

AUROC Area under the receiver operating characteristic curve

Positive correlations were seen among RVFW strains at the base, mid and apical segments with respect to both RV end-systolic area and RV end-diastolic area. In contrast, less robust negative correlations were seen among RVFW velocities at the base, mid and apical segments with respect to both RV end-systolic area and RV end-diastolic area. When analyzing these same TDI variables with indexes of RV systolic function, strain measured in the mid and apical segments correlated more with both RVFAC and TAPSE than with RVFW velocity. No significant difference was noted between RVFW strain and velocity when measured at the base.

A stepwise multivariate analysis using all the TDI variables was performed and, among strain and velocity indexes along the RVFW, mid RVFW ($P<0.002$; 95% CI 0.53 to 0.82) and apical RVFW ($P<0.002$; 95% CI 0.52 to 0.82) strain were the only two independent variables statistically associated with PH.

Finally, ROC curves were constructed using strain generation and myocardial velocity parameters measured at the RVFW base, mid RVFW and apical RVFW segments. Table 2 lists specific values for both strain generation and myocardial velocity (along with their respective 95% CIs and areas under the ROC curve) at the base, mid RVFW and apical RVFW portions that identify PH from normal controls.

DISCUSSION

In the present study, peak longitudinal strain and velocity data were collected from three different segments (basal, mid and apical) along the RVFW from normal individuals and from PH patients. After analyzing a total of 144 RV segments, we found that RVFW strain values in individuals without PH were higher in the mid and apical segments than in the basal segment. In contrast, RVFW strain in PH patients was higher in basal segments and diminished toward the apex. In terms of RVFW velocities, both groups showed decremental values from basal to apical segments. Basal and mid RVFW velocities were significantly lower in PH patients than in individuals without PH. Finally, of all the TDI variables analyzed, only mid and apical RVFW strain values were found to be independent predictors of PH.

Two-dimensional echocardiography has commonly been used in the management of PH patients. Unfortunately, it has several known limitations including suboptimal windows to delineate RV endocardial borders as well as the fact that the complex and eccentric shape of the right ventricle prevents the use of standard volumetric methods (24). However, TDI has introduced the analysis of regional myocardial velocity and strain, which have proven to be useful (25-27). In addition, to facilitate the assessment of ventricular function, TDI also offers the opportunity to identify the presence of mechanical delay or dyssynchrony. This has been extensively studied in the left ventricle (28-32) and our laboratory was the first to demonstrate the presence of RV dyssynchrony in patients with chronic PH (17).

TDI is an established method of tracking myocardial displacement and allows for the measurement of both myocardial velocities and strain (4,33-35). Myocardial velocities are derivatives of position with respect to time and describe the overall motion of all segments (36). Strain is a dimensionless quantity and is produced by the application of stress resulting in either lengthening (expansion) or shortening (compression) (37). A computerized algorithm calculates spatial differences in tissue between neighbouring samples within the myocardium aligned along the Doppler beam. Strain is obtained by integrating strain rate over time and represents the deformation of a tissue segment over time. Strain is expressed as the percentage change from the original dimension (34). Because regional contractility of individual myocardial regions is relatively uniform, measurements of strain as opposed to velocity facilitate differentiation of normal from abnormal contractility (34).

In a study of healthy individuals, Kukulski et al (7) demonstrated the presence of a baso-apical gradient for longitudinal velocities, while strain values showed an apex-to-base gradient. Although other RV TDI studies of patients with PH have not made any particular distinction of these differences, most of these studies combined values from different regions of the right ventricle when reporting their results (38-41).

Our results are concordant with previous data showing that systolic strain is more effective than velocity in predicting RV function based on the ability of strain to be less affected by tethering of adjacent myocardial segments, translation and cardiac rotation (34,42-44). In fact, peak systolic strain and strain rate, particularly of the basal RVFW, were recently suggested as the best index of RV function in patients with PH (43). However, our results go beyond these findings and suggest that

when different RVFW segments are taken into account, abnormalities in strain generation in the mid and apical RVFW portions are affected most in PH. In fact, strain values in these regions were the only two TDI variables that could independently predict PH. It could be argued that the more apical segments have less deformation due to the delayed myocardial activation that occurs with being closer to the right bundle than the basal segments (45). Finally, our results also highlight the importance of taking into account this difference in strain generation along the RVFW in PH when interpreting data. Not only is it important to recognize that this difference exists, it is also important to avoid combining values; they should be reported separately.

Limitations

The small number of patients is a limitation of the present study, which curtails our ability to generalize these findings to a larger population of patients with PH. In addition, invasive hemodynamic data were not obtained to correctly identify PASP; however, the patients included in the present study had documented disease and were followed at our PH clinic. The aim of the study was to identify whether there were any differences in terms of myocardial strain and velocity on the RVFW in patients with PH. Finally, we did not analyze the effect of different loading conditions that, by themselves, can affect longitudinal muscle shortening. However, we have demonstrated that the increased afterload associated with PH has a greater effect on RV longitudinal muscle shortening than that observed with changes in loading conditions (17,18).

CONCLUSIONS

Based on these results, it appears that significant alterations in strain generation occur along the RVFW in patients with PH. Of these abnormalities, the reduction in strain from mid and apical RVFW segments is found to be most predictive of PH. It is therefore important to be aware of these differences in strain generation when studying the effect of PH on the right ventricle. Additional studies are required to determine whether these differences are due to RV remodelling.

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